

THE ROAD TO PREFILLED DEVICES IN NOVEL COMBINATION PRODUCTS

In this article, Lior Shtram, Senior Director, Design & Engineering, Flex, discusses three approaches to delivering novel combination products – user-filled, user-loaded and prefilled – through the lens of sterilisation processes and requirements at the industrial manufacturing scale.

INTRODUCTION

In recent years, developments in pharmaceutical markets have been driving the introduction of novel drug delivery methods. Biologic products are presenting new challenges that mean they cannot be delivered conventionally. These challenges are presented by technical requirements such as high viscosity and large volume. Considering volumes of ≥ 3 mL, a prefilled syringe (PFS) solution becomes cumbersome and inconvenient. The high frequency of the therapy exacerbates the problem, creating the desire for a patient-centric device to deliver therapy at home. To meet these requirements, we are seeing the development of novel combination products such as electromechanical autoinjectors and on-body injectors.

Potentially these types of injectors could be offered in either user-filled, user-loaded or prefilled configurations. The first two configurations require user involvement and are prone to use errors and interface (leakage) issues. The prefilled option eliminates most of these potential use errors, providing a simpler and more effective experience for patients.

One of the key challenges created by these novel combination products is sterilisation. While sterilisation is a key factor for every medical device and drug delivery product, previous-generation combination devices already have established solutions that are well accepted in the industry by all parties. However, when introducing new drug delivery methods, sterilisation presents a unique challenge as it involves not only the device designer, but also the pharmaceutical company, the fill/finish CMO, automation suppliers and quality engineers.

It is possible to look at this challenge as a meeting point between two industries with conflicting processes – medical devices and pharmaceuticals. The device industry is accustomed to manufacturing sterile devices by producing and assembling the

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device in a clean environment and then sterilising the product after assembly. The pharmaceutical industry, however, follows a different process, in which the primary container of the drug is delivered pre-sterilised and the drug product is filled in an aseptic setting. The finalised product cannot withstand another sterilisation cycle, as that affects the drug product and can introduce additional risks. The two processes described are obviously incompatible and present a major challenge in providing novel integrated combination devices, such as a prefilled autoinjector.

USER-FILLED

The immediately obvious solution is to keep each industry separate, each continuing with its own established and respected processes (Figure 1). This solution leads designers to offer products that are user-filled. Here, the drug and the device are presented to the user in separate packages and the user is required to fill the drug product into the delivery device. Products that follow this principle already exist on the market, most notably in disposable devices for insulin. Doing so means that processes for sterilisation are already in place; the supply chain of each manufacturer is maintained; the device



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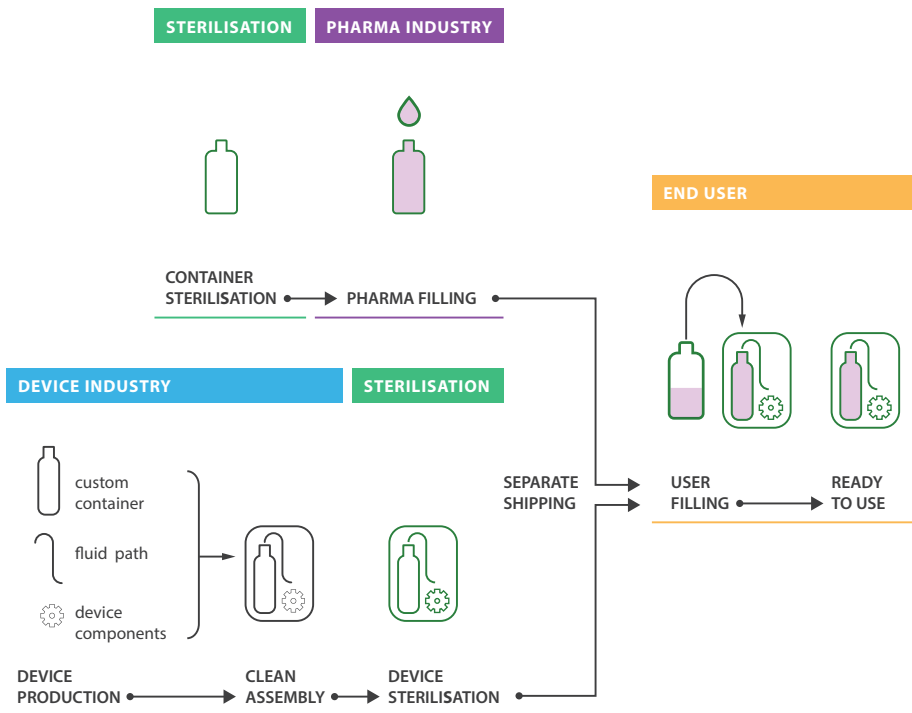


Figure 1: Assembly process for user-filled products.

manufacturer is not requested to handle the drugs and the drug filler is not requested to perform assembly operations. The advantages of this solution are significant to the commercial parties, not only from a technical perspective, but also from those of quality, liability and risk management.

Yet, from a human factors point of view, the solution of a user-filled device is severely lacking. The user is requested to utilise either an external vial and syringe or a PFS to inject the drug into the device. In certain cases, the drug is supplied in a vial and needs to be first drawn from the vial before injecting into the device.

In very specific use cases and requirements, the healthcare market might find this solution suitable. Consider the case where one would like to preserve the role of the healthcare provider (HCP) in the process of injection, while still avoiding IV injection and shortening the hospitalisation duration. This model is already employed in certain oncology applications with great success. However, these could be exceptions

that prove the rule. In most cases, the need for device filling creates additional use steps that are considered demanding for a non-professional user/patient.

Several solutions have been suggested to address this problem and to simplify the operation from the user's perspective. With this type of solution, we can include devices such as automated filling stations. Strictly speaking, filling stations do not reduce

the number of user steps, and therefore are not removing the burden from the user. Filling stations do overcome specific usability issues, such as reducing dexterity requirements. But more significantly, these solutions reduce possible errors and therefore try to limit the liability for the therapy provider. The attempt to solve a problem that is itself a by-product of a specific design problem with additional devices is far from ideal. The additional filling device is yet another device to design, ship and service, with its own specific costs, risks and liabilities.

USER-LOADED

A hybrid approach, that we shall refer to as user-loaded, has already been adopted in a few devices and could offer a small advancement towards improved usability (Figure 2). In this approach, the drug delivery device and the drug product are still delivered separately, however the drug product is provided to the patient in a custom container that fits as-is inside the drug delivery device. The custom container could be a custom primary container, as in the case of specific wearable devices, or else a custom secondary container, as is sometimes employed in smart electromechanical autoinjectors.

The assembly of the two components, delivery device and drug container, is still an extra step that is expected to be

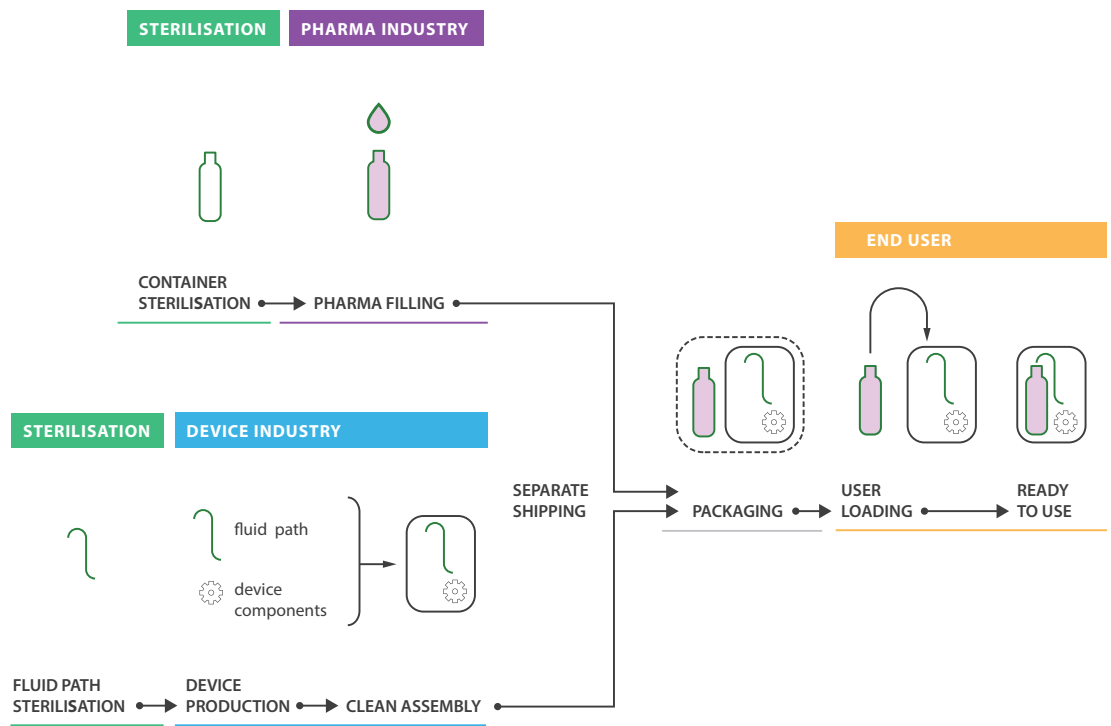


Figure 2: Assembly process for user-loaded products.

“While there is no necessity to use a custom container for the user-loaded device, in practice specific design considerations tend to drive designers toward these solutions.”

performed by the patient. This solution is straightforward and sensible in reusable delivery devices (as could be the case in expensive electromechanical autoinjectors), but from a usability point of view could still be considered cumbersome in single-use disposable devices.

The advantages of the user-loaded approach are self-evident. From a provider point of view, the advantages previously mentioned of the user-filled solution are maintained – separate supply chain, each supplier works with well-established processes and maintains the presently known liability, quality control and risks. From the patient point of view, it is obvious that a simple insertion of a primary container into a designated slot in the delivery device could be much simpler than handling a syringe. Still, in most cases, the patient will be requested to perform quite a few actions.

Overall the approach is still inferior to prefilled devices, considering the design and manufacturing implications of a custom drug container; non-standard containers increase the complexity of the development and validation of the solution with key issues such as materials compatibility

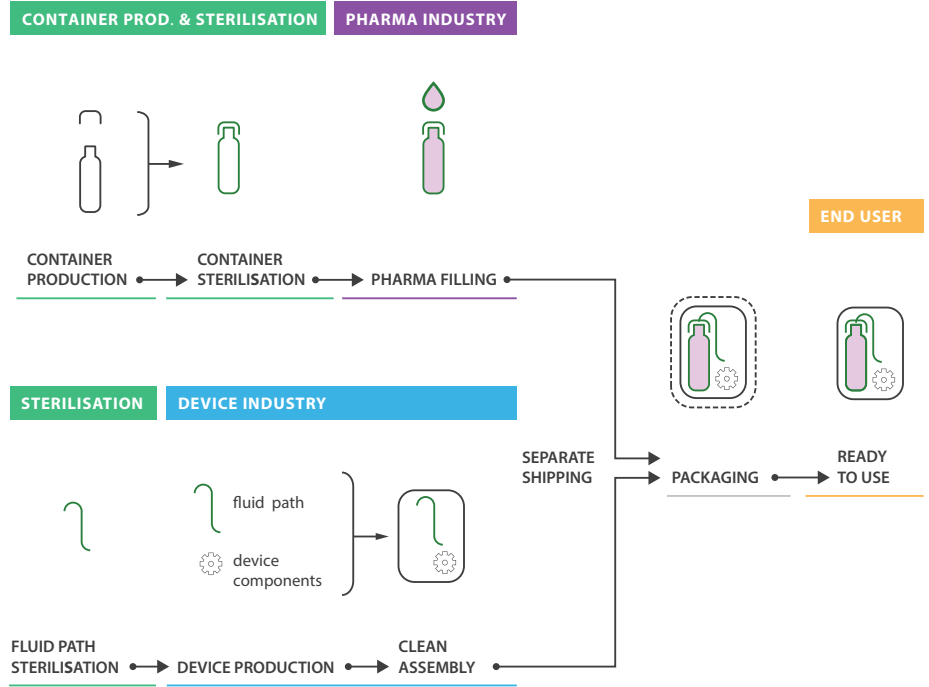


Figure 3: Assembly process for prefilled products.

and drug stability. While there is no necessity to use a custom container for the user-loaded device, in practice specific design considerations tend to drive designers toward these solutions. User-loaded devices that employ completely standard drug containers are a rare breed.

PREFILLED

While the user-filled and user-loaded solutions provide current viable solutions, there is still a pressing need for a better design. With ever more products requiring regular delivery at home, human factors become central to the design of the

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device. A desire to simplify and reduce the number of steps for the patient will likely eventually drive the market towards prefilled solutions. In this sense, once achieved in the market, prefilled solutions would set the bar for future products. It is therefore interesting to explore in depth the possibilities of such prefilled design options (Figure 3).



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The immediate solution one could suggest would be to integrate the device and drug container at the filling site. Sterilised items are received into the aseptic core and could potentially be assembled into a complete unit. However, such secondary operations are expensive from the filling line perspective. These manufacturing lines require major investments into capital expenses, time to deploy and validation efforts. The approach might be technically feasible but strong business cases are required to justify the significant investments and thus, in most cases, the approach will be rejected by the relevant parties. It is important to note at this point that existing solutions that require device assembly after filling, such as PFS, do not require the assembly to be performed in the aseptic core. This is a major difference that presents a unique challenge, especially in the case of on-body injectors.

Another approach would take only essential elements into the aseptic core. These include the primary container and any element of the fluid path that would be in contact with drug. Keeping the rest of the delivery system external to this process does somewhat simplify the adjustments required of the aseptic core and filling line. Any modification of the primary container also impacts the way in which containers can be filled. Consider the addition of a fluid path in the case of an on-body injector, such a fluid path is required, at a minimum, to provide means of delivery perpendicular to the length axis of the tube. Fitting this bulky fluid path into a nest & tub setup requires adjustments and reduces the efficiency of the filling line.

Additionally, the two components of the design, the sterile container-fluid-path and the non-sterile device, require a box level assembly step. If the box level build is to be done at the device contract manufacturer,

that manufacturer would need to handle drugs and comply with the relevant quality requirements. Thus, the disadvantages of the approach include a custom primary container, some modification to the filling process as well as drug handling requirements at the top-level assembly.

Yet another design approach would keep both device and pharma processes as they are. In this case, the fluid path that is part of the device would be sterilised after device assembly but before the assembly of the sterile primary container filled with the drug. Here, the connection between the container and the device becomes the key challenge of the design. This connection needs to guarantee sterility from the container and throughout the fluid path, and yet keep sterility after device sterilisation, through drug container assembly and up until the injection occurs.

A specific variant of the previously mentioned solution would solve the connection sterility problem by local real-time disinfection. A disinfection solution would emulate the current practices of injections by an HCP. Apart from the challenge of coming up with a viable real-time disinfection method, the major implications of real-time disinfections would revolve around transferring the liability of the disinfection process to the pharmaceutical company and placing the onus of validation on the device designer.

In the future, it might be possible to simplify the sterilisation challenges as new sterilisation processes are being developed that show promise in avoiding degradation of the drug product. Several

suppliers have already made claims that their newly developed sterilisation process reduces risk and allows for the sterilisation of a combination product after filling. Considering the time scales the pharmaceutical industry tends to work on, we can expect adoption of these methods to take several years.

FINAL THOUGHTS

There are several key challenges to providing an effective solution to the market need for prefilled injectors. Solving these challenges is key to enabling the continued and successful expansion of home-based, patient-centric delivery systems that promise to deliver on the promise of ease of patient compliance, reduction of dosing and usage errors, and ultimately better and cost-effective care for patients.

In addition to the challenges presented by the development of a prefilled smart injection system concerning sterilisation, there are other areas to be fully developed. These are outside the scope of this article – and include considerations such as human factors, regulatory, certification, liability of the individual contributors in the supply chain and organisational challenges. However, a tight collaboration between all the stakeholders in the industry (device manufacturers, pharma company, fill finish CMOs, automation suppliers) will unlock the full potential of this category of devices.

Selection of the right partners is key to success by defining and addressing critical considerations from the beginning, so the right solution can be developed with full visibility to the challenges and the requisite experience can be employed to solve those challenges proactively. The clear need for the device category is present, and companies are responding with innovative solutions demonstrating the path to overcome the challenges that have been discussed in this article.

ABOUT THE COMPANY

Flex is the Sketch-to-Scale™ solutions provider that designs and builds Intelligent Products for a Connected World™. With approximately 200,000 professionals across 30 countries, Flex provides innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to companies of all sizes in various industries and end-markets.

ABOUT THE AUTHOR

Lior Shtram is a Senior Director of Technology Management at Flex, which provides design, development, and manufacturing services for medical devices deploying the expertise of design teams and subject matter experts around the world. He has more than 10 years of experience designing and developing novel medical devices, helping to bring to market many diagnostic and therapeutic devices and drug delivery systems. Mr Shtram is based in Israel.